

Repeat Screening for HIV: When to Test and Why

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Summary: This paper presents models for repeat HIV screening under conditions of constant low HIV incidence. The models reveal a direct link between the prevalence of undetected HIV infection and the screening interval between repeat HIV tests. We show how to select screening intervals that either achieve a given HIV prevalence level, or optimally balance the cost of repeat HIV testing against the cost of HIV infection. Alternatively, given an existing repeat screening program, the model implies that cost of infection for which the given screening interval is optimal. The method also suggests how to select an HIV testing technology. The models are applied to existing repeat testing programs in the U.S. Army and among legal commercial sex workers in the state of Nevada in the Far West of the United States. **Key Words:** HIV screening—Repeat screening—HIV prevalence—Mathematical model—Cost-benefit analysis.

Throughout the history of the HIV/AIDS epidemic, certain populations have been subject to repeat HIV testing. These include, but are not limited to, commercial sex workers (CSWs) and people in military service. The reasons for such testing vary; CSWs are typically screened because they are potentially at high risk for the transmission and acquisition of HIV (1–3), whereas people in military service are considered part of a “walking blood bank” (4,5).” In some sense, people in the general population who engage in high risk behavior and regularly have themselves tested also constitute a repeatedly screened population.

In designing any repeat HIV testing program, the following two questions must be addressed: how often should people be tested, and which test should be used? Even those in the general population make these choices given the availability of home testing, publicly funded anonymous counseling and testing sites, and testing through private physicians. This paper addresses these two questions with the aid of a simple economic model. We assume that undetected infections are costly, and identify a “cost of infection” c per person-year of unde-

TECTED infection in the population. Given such cost, and given the costs of testing, it is possible to design testing strategies that optimally balance the cost of undetected infections (which decreases with increasing test frequency) and the cost of testing itself (which increases with increasing test frequency). The models in this paper thus differ from descriptive HIV screening models intended to estimate the cost-effectiveness of HIV testing per se (6,7) and are much simpler than existing prescriptive screening models in the literature (8,9).

An alternative use of our proposal is to evaluate existing repeat testing programs with an eye toward determining their implied costs of infection (c). For example, brothel-based CSWs in Nevada are tested for HIV monthly (10), regulated CSWs in Victoria, Australia are tested quarterly (11), and active duty soldiers in the US Army are tested on average every 1.4 years (4,12). Given the HIV incidence, the assay used, and the cost of carrying out the testing, each of these schedules is an optimal strategy for some cost of infection c per person-year of undetected HIV infection. Calculating these implied costs provides a tool for evaluating an existing strategy and also allows comparisons across strategies in different populations. In addition, our approach can determine whether a change in assay could achieve the same goal at a lower cost.

In the second section of this paper, we show how to

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estimate the prevalence of previously undetected HIV infection. In the third section, we present two approaches for selecting the screening intervals (the time between HIV tests). We next show how to select among competing HIV testing technologies in the fourth section. In the final section, we illustrate our approach using two examples of repeatedly screened populations: regulated (brothel-based) CSWs in Nevada and active duty personnel in the U.S. Army.

MODELING THE PREVALENCE OF UNDETECTED HIV INFECTION IN REPEATEDLY SCREENED POPULATIONS

Consider a population subject to repeat HIV screening. We assume that community members are HIV negative on entry. This is a reasonable assumption in the two cases considered in this paper. Regulated CSWs typically require proof of HIV negativity (as is the case in Nevada [10] and Victoria, NSW [11]), whereas the U.S. Army, which screens all recruits, does not accept individuals who test positive for HIV (4). We seek to determine the prevalence of *previously undetected* HIV infection in the population. This does not necessarily correspond with overall HIV prevalence, because different rules apply in different circumstances when a person is found to be infected with HIV. For example, HIV-positive regulated CSWs are typically *required* to cease working after their infection status has been determined (10,11), in which case *all* HIV infections in the population at any time have yet to be detected. By contrast, known HIV-positive soldiers in the U.S. Army, although not stationed outside the United States and no longer eligible for blood donation, are monitored medically and allowed to remain on active duty so long as their health permits (4). Overall HIV prevalence in this circumstance is the sum of known and previously undetected infections.

We assume that susceptible members of the population in question become infected with HIV at the constant incidence rate of r new infections per uninfected individual per unit of time. The repeat screening policy, either as a matter of suggestion or regulation, calls for individuals to be tested for HIV once every τ time units. We refer to τ as the *screening interval*. The screening test employed is characterized by a window period of mean duration w during which HIV-infected persons would test negative due to the test's inability to detect recent infections. We assume that HIV testing is perfectly sensitive following expiration of the window period, a reasonable assumption for the HIV tests considered in this paper (13–15).

Now suppose a person becomes infected with HIV.

How much time will pass until this infection is detected through the repeat screening process? Clearly, the window period must expire, which requires w time units on average. However, in addition, an expected $\tau/2$ time units will pass until the first HIV test following the completion of the window period, given that timing of new infections is random with respect to the fixed repeat screening process (which calls for tests once every τ time units from entry into the population). Consequently, newly infected individuals will be detected through repeat screening an average of $w + \tau/2$ time units after the moment of infection.

What is the resulting level of undetected HIV infection in the population? Assuming that HIV incidence remains constant and equal to r , let p denote the prevalence of undetected HIV infection in the population, and p_d denote the prevalence of previously detected HIV infection in the population. Stability requires that the prevalence of undetected infection p must satisfy a “prevalence = incidence \times duration law”¹⁶

$$p = (1 - p - p_d) \times r \times (w + \tau/2) \quad [1]$$

Assuming that the prevalence of previously detected HIV infection p_d is small (which is clearly the case if those infected and detected are removed from the population, as is the case with regulated commercial sex workers), Equation 1 implies that the prevalence of undetected HIV infection p is approximately given by

$$p = \frac{r \times (w + \tau/2)}{1 + r \times (w + \tau/2)} \quad [2]$$

When the HIV incidence rate itself is small (as has been observed where commercial sex work is legal and regulated), the prevalence of undetected HIV infection in the population can be very well approximated by

$$p = r \times (w + \tau/2) \quad [3]$$

(which literally reads as “prevalence = incidence \times duration”). Equation 3 remains a valid approximation even if infected individuals are not removed from the population, providing the *overall* prevalence of HIV infection $p + p_d$ remains sufficiently small (e.g., less than 1%, which is the case for active duty soldiers in the U.S. Army), for in this circumstance Equation 1 collapses directly into Equation 3.

Equation 3 highlights the impact of repeat screening on the prevalence of unknown HIV infection. Increasing the frequency of repeat screening serves to lower the time interval τ between screening tests, which in turn lowers the prevalence of undetected HIV in the population. Similarly, the employment of tests with shorter win-

dow periods (such as nucleic acid tests based on the polymerase chain reaction) would lead to lower prevalence of undetected HIV infection than tests with longer window periods (such as antibody tests).

SELECTING THE SCREENING INTERVAL

Achieving an Acceptable Level of Risk

One approach to selecting a screening interval is to specify the largest prevalence of undetected HIV infection that can be tolerated in the population, and then solve for the implied screening interval. Toward this end, Equation 3 can be rewritten as

$$\tau = \frac{2}{r}(p - rw) \tag{4}$$

where p now represents the “target” prevalence of undetected infection. This expression accords well with intuition; the screening interval decreases as the HIV incidence rate r increases (so higher incidence calls for more frequent screening), increases with the undetected HIV prevalence target (so that the higher the acceptable undetected HIV prevalence, the less rapid the screening), and decreases as the mean window period increases (so that less sensitive tests require more frequent screening).

Maximizing Net Public Health Benefits

From the standpoint of public-health decision making, programs should ideally be designed to maximize their resulting public health benefits minus the costs of program operations. In the context of repeat screening for HIV, benefits result from reducing the prevalence of undetected HIV infection, whereas the costs are those of the screening tests themselves (as well as attendant counseling costs when such counseling accompanies HIV testing). The benefit of reducing undetected HIV prevalence can be reexpressed as a cost per infected individual per unit of time that applies over the time period during which a person is HIV infected but has not been identified as such through a screening test. Note that this cost reflects the missed opportunity for infected individuals to pursue early medical and social interventions on account of not knowing their infection status, in addition to the increased risk of HIV transmission from infected individuals to others.

Letting c denote the cost of infection per undetected infected individual per unit time and k denote the cost of counseling and testing per screening visit, the total public health cost per person per unit of time associated with a

repeat screening policy with a screening interval τ between visits, $TC(\tau)$, is given by

$$\begin{aligned} TC(\tau) &= c \times p + k/\tau \\ &= c \times r \times (w + \tau/2) + k/\tau \end{aligned} \tag{5}$$

where we have used Equation 3 to estimate the prevalence of undetected HIV infection. The first part of Equation 5 covers the cost of infected but undetected individuals per unit of time, whereas the second part covers testing costs per unit of time, noting that if the screening interval equals τ , the screening rate equals $1/\tau$ tests per person per unit of time.

The optimal screening interval τ^* is that quantity that minimizes total public health costs, and is given by

$$\tau^* = \sqrt{\frac{2k}{cr}} \tag{6}$$

This result also accords well with intuition; the optimal screening interval declines with increases in either the HIV incidence rate (r) or the cost of undetected infection (c), whereas the optimal screening interval increases with the cost of HIV testing (k).

One might argue that the cost of infection c should actually depend on the prevalence of undetected infection p in the screened population. Consider CSWs as an example. The cost of infection should reflect, among other things, the number of infections that could be transmitted by an infected CSW. This number depends on the HIV prevalence in the unscreened population of clients (for an infected CSW cannot newly infect someone already infected). And, to the extent that new HIV infections in the population of clients derive from infected CSWs, the prevalence of HIV in the unscreened population will depend on the level of HIV among CSWs. However, in situations where both the incidence and prevalence of HIV are low and stable among CSWs, the effect of such interdependence between the cost of infection c and the prevalence of undetected HIV p could not be large. It is therefore reasonable to allow c to remain constant when modeling scenarios such as those in this paper, where the incidence and prevalence of HIV remain stable and low.

CHOOSING AN APPROPRIATE SCREENING TEST

Public health authorities that choose (or are required) to implement repeat screening programs for HIV should strive to provide programs that are not only effective, but also efficient. In addition to choosing the screening interval for repeat screening programs, public health offi-

cials can also determine which screening test to use. Different screening tests are characterized by different window periods and different costs. Typically, the shorter the window period (and the greater the effective sensitivity), the more expensive the test will be. Although the optimal screening interval given a particular testing technology does not depend on the duration of the window period for the test in use, total public health costs do. Substituting Equation 6 into Equation 5, the total public health costs using the optimal screening interval τ^* are given by

$$TC(\tau^*) = c \times r \times w + \sqrt{2 \times k \times c \times r} \quad [7]$$

Now consider the choice between two possible screening tests. The first (second) test is characterized by a mean window period of duration w_1 (w_2) whereas the cost of testing per visit is given by k_1 (k_2) for the first (second) test. Employing the first test should be preferred to the second if the total public health costs using the optimal screening interval for the first test are lower than for the second. The first test should thus be used if $TC(\tau^*_1) < TC(\tau^*_2)$, which occurs when

$$cr < 2 \left(\frac{\sqrt{k_1} - \sqrt{k_2}}{w_1 - w_2} \right)^2 \quad [8]$$

Similar comparisons can be made to decide which of several testing methods is most appropriate for any given situation.

EXAMPLES

Regulated Commercial Sex Workers in Nevada

To illustrate the use of these models, we first consider legal, regulated prostitution in Nevada. Existing regulations require CSWs to obtain work permits. To obtain such a permit, applicants must first test negative for gonorrhea and chlamydia (and continue to test negative at weekly screenings), as well as for syphilis and HIV (with negative tests required monthly as a condition for continued employment) (10). Very little research appears to have been conducted regarding HIV prevalence and incidence among Nevada's legal CSWs, but available studies all point to extremely low rates of HIV in this population (1). Of particular note are data describing 440 different CSWs who were tested monthly through a local county health department screening program between 1990–1995 (17). The average time between first and last HIV tests for these CSWs was 609 days, implying a total exposure time of 733.6 years across all 440 CSWs. No incident infections were observed in this study. Because the probability of observing no incident infections over

733.6 years of exposure when the true HIV incidence rate equals r is given by $e^{-733.6r}$, the data imply a one-sided 95% confidence interval estimate for the true incidence rate of zero through 4 infections per 1000 person years. We therefore set $r = 0.004/\text{yr}$ to represent HIV incidence among regulated Nevada CSWs, recognizing that this is in all likelihood an overestimate of the true HIV incidence rate.

The first question is, given this incidence (over)estimate, what is the implied HIV prevalence? Because HIV testing was conducted with licensed enzyme immunoassay tests (EIA) in Nevada (17), the appropriate average window period w to use for our calculations is 45 days (or 0.12 years) (13). Moreover, given that Nevada policy requires monthly HIV testing, we set $\tau = 1$ month (or 0.08 years). Direct application of Equation 3 then yields an undetected HIV prevalence estimate of

$$p = 0.004 \times (0.12 + 0.08/2) = 0.0006 \quad [9]$$

or 6 in 10,000, a low figure consistent with the paucity of reported cases of HIV among regulated Nevada CSWs.

Suppose that health officials were willing to entertain an undetected HIV prevalence of 1 in 1000. What level of HIV screening would be required? Setting $p = .001$ in Equation 4 reveals that the new screening interval should equal

$$\tau = \frac{2}{0.004} \times (0.001 - 0.004 \times 0.12) = 0.26 \text{ years} \quad [10]$$

or roughly 3 months. Even though adoption of quarterly screening would reduce testing costs by a factor of 3 compared with monthly testing, such cost savings might not be viewed as sufficient to warrant an increase in undetected HIV prevalence among CSWs from 6 to 10 in 10,000.

If health officials were willing to specify the annual cost of infection per infected CSW (c), Equation 6 could be used to select the optimal screening interval. Figure 1 reports the screening interval as a function of c , assuming that the cost of an HIV antibody test (k) equals the \$5.00 (all amounts given in U.S. dollars) actually charged by the state laboratory in Nevada that performs about half the tests from regulated CSWs (Randall Todd, Bureau of Disease Control and Intervention Services, State of Nevada, personal communication), and that annual HIV incidence among CSWs equals 0.004. Note that when the annual cost of infection equals \$360,000, the optimal screening interval τ^* equals 1 month, the current policy. This reveals an implicit valuation of the annual cost of infection, in that the current screening interval in Nevada has been selected as *if* the cost of infection was believed

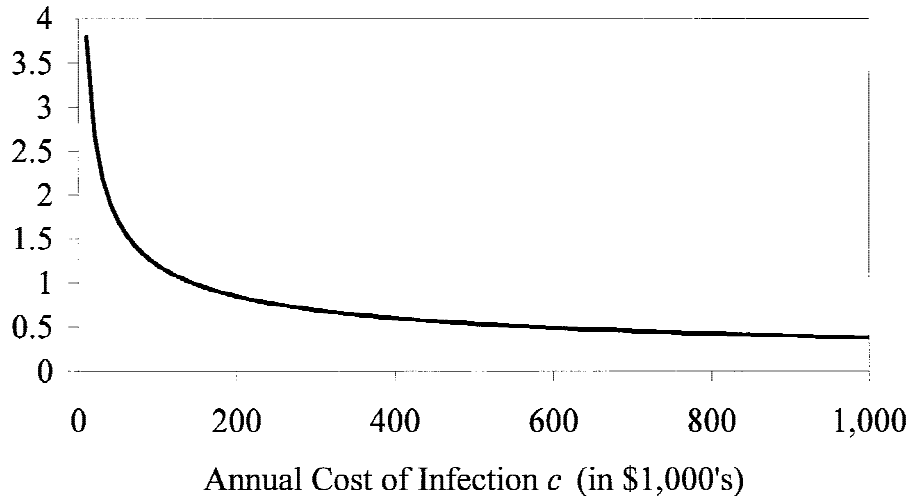


FIG. 1. Optimal screening interval τ^* (in months).

to equal \$360,000/infected CSW/year. If the cost of infection was judged to be as low as \$10,000 annually, then HIV testing twice per year would suffice. At the other extreme, the annual cost of infection would have to equal \$1.44 million before twice monthly HIV testing would become optimal.

Note that this implicit valuation assumes an HIV incidence rate r of 0.004 per year among Nevada CSWs. However, as stated earlier, this estimate is the outer limit of a 95% confidence interval based on observing no infections over 733.6 CSW years of exposure. A lower incidence estimate would force the implied cost of infection to be even higher to justify monthly HIV screening of Nevada CSWs.

One way to scale the annual cost of infection is to consider that the present value of medical costs alone for new HIV infections has been estimated to equal approximately \$200,000 (18). Setting the cost of one infected CSW equal to \$1 million per year would thus be equivalent to the medical expenses for 5 new HIV infections. At the implied \$360,000 annual cost of infection estimated for CSWs in Nevada, the equivalence is to medical costs for 1.8 new infections. Given existing regulations regarding the use of condoms and other safer sexual practices in Nevada's regulated commercial sex industry along with evidence suggesting that these regulations are upheld (1,17), the number of new infections that would be transmitted during 1 year of exposure to infected CSWs might well be as low as the figures above.

Active Duty Soldiers in the U.S. Army

The U.S. Army screens all active duty soldiers, with roughly 70% of the force screened annually, which amounts to a screening interval of $\tau = 1.4$ years or

roughly 17 months (4,12). Army researchers report the detection of approximately 150 new HIV infections each year (4). This enables an estimate of HIV incidence among active duty soldiers as follows: of approximately 500,000 active duty soldiers (12), 70% are screened in any year. However, each of those screened was last tested 1.4 years earlier, leading to a person-time contribution of $500,000 \times 0.7 \times 1.4 = 500,000$ person years (where we have ignored the negligible impact of known HIV positives and seroconverters in calculating person years of exposure). The estimated incidence of new infections among active duty U.S. Army soldiers thus equals $150/500,000 = 0.0003$ new infections per uninfected person per year. We will use this as our estimate of r .

The Army has also used standard EIA testing, so we continue to estimate the mean window period w as 45 days (0.12 years). We can now determine the prevalence of undetected HIV infection among active duty soldiers using Equation 3. The result is

$$p = 0.0003 \times (0.12 + 1.4/2) = 0.00025 \quad [11]$$

or 2.5 in 10,000. This is *much* lower than published prevalence rates of 1.3 to 1.7/1000 soldiers (4), indicating that most HIV infections among active duty soldiers in the U.S. Army have been identified.

Whether this repeat screening policy is a reasonable use of public funds can be examined by considering the implied cost of infection. The testing cost k has fallen from \$4.41 during the initial 6 months of the testing program to \$2.52 per sample (4). If the existing screening interval of 1.4 years corresponded to an optimal decision, then inverting Equation 6 and solving for the cost of infection c yields the result

$$c = \frac{2k}{r\tau^{*2}} = \frac{2 \times 2.52}{0.0003 \times 1.4^2} = \$8,570 \quad [12]$$

If the actual annual cost of infection is believed to fall below this amount, then one could argue on economic grounds that the U.S. Army is overscreening the force. Alternatively, if the cost of infection is believed to exceed \$8,570, then on economic grounds one could argue that more frequent screening is warranted. Note that the \$8,570 implied cost of infection for active duty soldiers falls far below the implied annual cost of \$360,000 estimated for regulated Nevada prostitutes.

Now consider the question of which HIV testing method to use. Table 1 reports the mean window periods and costs for four different HIV testing technologies: standard EIA antibody testing (EIA), third generation combination tests (COMBI), p24 antigen (Ag), and polymerase chain reaction (PCR) (4,19). Applying the inequality 4.2 to the data in Table 1 while retaining our working assumption that the HIV incidence rate r among active duty soldiers equals 0.0003 annually reveals that EIA testing should be preferred to COMBI testing providing that the annual cost of infection c is less than \$707,310. Similarly, antigen testing should be preferred to PCR if $c < \$6.99$ million, and EIA is preferable to PCR if $c < \$3.13$ million. Taking all possible test combinations into account, these results imply that antigen testing is *never* efficient for the repeat testing of active duty soldiers in the U.S. Army without regard to the cost of infection. If the cost of infection c is less than \$707,310, EIA testing should be employed. For values of c that fall between \$707,310 and \$13.8 million, COMBI testing would be most efficient. For values of c in excess of \$13.8 million, PCR should be used. Moreover, the \$8,570 annual cost of infection implied by current U.S. Army policy falls well within the range of c values for which EIA testing is the optimal choice.

DISCUSSION

The models in this paper should prove useful to those interested in designing or reconsidering repeat HIV screening programs. We have considered the repeat test-

ing of regulated CSWs and active duty personnel in the U.S. Army as examples, but the methods are applicable to other populations as well. The models highlight the direct link between repeat screening and the prevalence of undetected HIV prevalence in the population and provide pragmatic tools for either selecting screening intervals and HIV testing methods, or reflecting on existing policy.

Throughout this paper, we have assumed that the HIV incidence rate remains low and constant in the population screened. In situations in which this assumption does not hold, our models would not be appropriate. For example, if HIV incidence rates were increasing in the population, and repeat testing only identified infected persons without slowing the rise in HIV incidence, then the rate of screening in the population should increase over time. Our models would prescribe underscreening in such a situation. However, as illustrated in this paper, there are populations in whom HIV incidence remains low but steady, and for these populations our models apply.

Although developed with mass screening programs in mind, the models also suggest a framework for broader counseling of HIV negative persons regarding whether HIV testing is warranted, and if so, how often. The risks associated with any individual's sexual or drug injecting behavior (or lack thereof) in a particular setting translate to that individual's HIV incidence rate, whereas the anxiety and uncertainty surrounding HIV testing (or lack thereof) translate as psychic HIV testing costs. In addition, there are costs to being HIV positive without realizing that such is the case (such as delayed access to HIV therapy). We contend that sorting through such competing concerns fits within the realm of problems HIV counseling is meant to address. Viewed in this light, our models offer a modest guide to the perplexed.

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TABLE 1. Mean window periods and costs of HIV tests

Test	Mean window ω (days)	Testing cost k (U.S. \$)
Standard antibody enzyme immunoassay (EIA)	45	2.52
Combination (COMBI)	22	5
p24 Antigen (Ag)	16	10
Polymerase Chain Reaction (PCR)	11	13

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